REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claim amendments

Claims 2-3, 9, and 17-23 were previously canceled without prejudice or disclaimer.

Claim 24 is being newly added. No new matter is added by the new claim. Support for the new claim can be found, for example, in claim 1 as previously presented and on page 17, in the table provided in the results section. The table clearly shows various ratios of the biocompatible polymer with the contrast agent including ratios between 0.07-0.182.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

After amending the claims as set forth above, claims 1, 4-8, 10-16, and 24 are now pending in this application.

Summary of claimed invention

Inconsistent visibility of the embolic compositions during catheter delivery can result in under-filling or over-filling of the vascular site to be embolized (see page 3, paragraph [0011] of the application as filed). The under-filling of the vascular site, such as in the case of an aneurysm, can result in an active aneurysm left in the patient. The over-filling of the vascular site can result in the overflow of the composition in the adjoining blood vessels leading to embolization of those blood vessels, or worse, embolization of body organs, such as brain (seepages 2-3, paragraph [0008]).

The art has disclosed the use of up to 40 weight percent of the contrast agent in the composition. Mere addition of additional contrast agent into the embolic composition in order to enhance fluoroscopic visibility poses several practical concerns (see page 4, paragraph [0013] of

the application as filed). The concerns include adequate flowability of the composition to avoid plugging of microcatheter or cause high injection pressure; formation of coherent precipitate *in vivo* to minimize fragmentation and possible embolization of unintended vascular sites; and health safety of the patient after administration of high amount of contrast agent (see pages 4-5, paragraphs [0014]-[0016]).

Inventors of the instant application, unexpectedly, found that the composition containing a higher concentration of the water-insoluble, biocompatible contrast agent along with a ratio of biocompatible polymer to the water-insoluble biocompatible contrast agent to be 0.07 or greater, retains the efficacy of the composition for endovascular surgical procedures by providing possessing adequate flowability through the microcatheter and forming a coherent precipitate *in vivo* without the undesired fragmentation and the shedding of the particles. *See* page 5, paragraph [0021] of the application as filed. Applicants note that the Declaration by Brian M. Strauss filed February 14, 2008, demonstrates that greater than about 40 to about 60% contrast agent and a ratio of biocompatible polymer to water-insoluble biocompatible contrast agent of greater than 0.055 (greater than 0.07 in instant amended claims) results in a polymer precipitate that is relatively cohesive and provides a high level of visualization during delivery. This is an improved composition over compositions taught by the art.

Therefore, it is critical for the composition to have both greater than 40 to 60 weight percent of water-insoluble, biocompatible contrast agent and the ratio of biocompatible polymer to the water-insoluble biocompatible contrast agent to be 0.07 or greater, in order to provide a composition with improved visualization, adequate flowability and cohesive precipitation.

Claim rejections under 35 U.S.C. §102(e)

Claims 1, 4-8, and 10-16 stand rejected under 35 U.S.C. §102(e) as being anticipated by Whalen et al. (US 2002/0090339, "Whalen" herein).

Applicants request the Office to reassess the appropriateness of the application of this rejection under 35 U.S.C. §102(e) based on the publication date of Whalen. Whalen's filing date

is October 11, 2001 and publication date is July 11, 2002. The priority date of instant application is March 7, 2003. Hence, Whalen does not qualify as prior art under 35 U.S.C. §102(e).

The Office alleges that the amount of contrast agent of greater than 40 to 60 weight percent and the ratio of biocompatible polymer to the contrast agent of 0.07 or greater is a result effective parameter that would be obvious to a person of ordinary skill in the art to routinely optimize. See pages 4 and 5 of the Office Action mailed on January 13, 2009.

Applicants submit that obviousness is not a correct standard for determining anticipation. Applicants will address this rejection in the claim rejection under 35 U.S.C. § 103(a) as below.

Nevertheless, Applicants traverse the rejection for the following reasons:

To anticipate a claim, a single source must contain all of the elements of the claim. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379 (Fed. Cir. 1986).

Whalen teaches a composition containing a biocompatible polymer at a concentration of from about 2 to 50 weight percent; a biocompatible contrast agent at a concentration of from about 10 to about 40 weight percent; and a biocompatible solvent from about 10 to about 88 weight percent.

Whalen does not teach any criticality of the ratio of the polymer to the contrast agent in the composition containing a higher concentration of contrast agent. Further, Whalen does not teach any definitive minimum ratio of the biocompatible polymer and the contrast agent, let alone a ratio of 0.07 or greater or 0.07-0.182 (claim 24). Even if the ratios are calculated based on the amount of biocompatible polymer and the contrast agent, the composition of Whalen will have the ratios anywhere from 0.05:1 (2/40) to 5:1 (50/10). There is no teaching in Whalen to pick a definitive minimum ratio of the polymer to the contrast agent, let alone pick and choose a ratio 0.07 or greater or 0.07-0.182, to arrive at the claimed invention. Therefore, the ratio of the biocompatible polymer to the contrast agent to be 0.07 or greater is neither expressly nor inherently disclosed in Whalen.

In *Ex parte Whalen,* 89 U.S.P.Q.2d 1078 (2008) (PTO Bd. App. & Int.) (precedential, attached as **Exhibit I**), an expanded panel of the Board, including Chief APJ Fleming, determined that the Examiner had not made out a case of inherent anticipation since the Examiner had not provided an adequate basis based on evidence or scientific reasoning to support that the compositions disclosed by Evans (prior art therein) inherently possessed the same viscosity as the claimed invention of Whalen. The Board further ruled that even though the Examiner reasons that Evans' compositions comprise similar components used in overlapping ranges of concentrations, it is not adequate to support a finding of inherent anticipation. *Id.* at 1083.

The Board cited with approval:

> "Inherency . . . may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981). *See also Ex parte Skinner*, 2 USPQ2d 1788, 1789 (BPAI 1986) ("[T]he examiner must provide some evidence or scientific reasoning to establish the reasonableness of the examiner's belief that the functional limitation is an inherent characteristic of the prior art" before the burden is shifted to the applicant to disprove the inherency.).

Id. Applicants submit that the Office has not provided any evidence or scientific reasoning to establish that the claimed ratio of 0.07 or greater or the ratio of 0.07-0.182 is an inherent characteristic of the teachings of Whalen. As explained *supra*, Whalen neither expressly nor inherently discloses the claimed ratios. As such, Whalen does not anticipate the currently claimed invention.

Further, Whalen does not teach a greater than 40 to 60 weight percent of a contrast agent, as in the claimed invention. The Office alleges that the concentration of "about 40 percent" of Whalen can be either 40 percent or greater than 40 percent.

First, Whalen does not teach or suggest that the term "about" is intended to increase the amount of contrast agent to > 40%. All the Examples of Whalen teach only 30 weight % of contrast agent which is outside the scope of instant claims.

Second, Applicants disagree with the Office's construction of the term "about." The Federal Circuit has ruled that the term "about" must be read relative to the use of the term in the specification of the patent. For example, the Federal Circuit in *Viskase Corp. v. American National Can Co.*, 261 F.3d 1316, 1322, 59 USPQ2d 1823 (Fed. Cir. 2001) ruled that the patents for heat-shrinkable multilayer thermoplastic compositions, which described a very low density polyethylene (VLDPE) copolymer film "having a density below about 0.91" grams per cubic centimeter, were not literally infringed by competitor's products containing a polymer with density of 0.912 grams per cubic centimeter.

The Federal Circuit ruled that:

> At a minimum, we conclude that a person knowledgeable in the field of polyethylene copolymers, reading the first family specifications and prosecution histories, would not view "below about 0.91" as extending to an upper limit of 0.914. Thus, we hold that the correct construction of the claims of the first family patents is that "below about 0.91 g/cm^3" means "below about 0.910 g/cm^3." We need not decide what range is reasonably encompassed in the "about" in "about 0.910," for in all events it can not reach films having a density of 0.912, a product at issue in this suit.

Id. at 1322.

Now turning to the teaching of the claims and specification in Whalen, Applicants submit that Whalen does not define any specific definition of the term "about." Whalen discloses a lower range of about 10 to about 40 weight percent in its claims and specification. All the Examples of Whalen disclose only the 30 weight % amount of the contrast agent which is not within the scope of instant claims. Example 2 of Whalen discloses a composition (comparative Example A) containing 8.5 weight % of ethylene vinyl alcohol copolymer and 30 weight % of tantalum (calculated ratio of 0.28:1) and a composition (composition of Example 2) containing 17.5 weight % of ethylene vinyl alcohol copolymer and 30 weight % of tantalum (calculated ratio of 0.58:1). There is no teaching in the specification of Whalen to use a greater than 40 to 60 weight percent of a contrast agent. A person skilled in the art, after reading the specification of Whalen, would not view the "concentration of from about 10 to about 40 weight percent" as extending the range recited to include "greater than 40 weight percent" as alleged by the Office.

Example 3 of Whalen discloses that the composition of Example 2 forms a more "ball-like" precipitate with significantly less migration under identical flow conditions as compared to the precipitate formed from the composition of Comparative Example A. Therefore, just a change in the concentration of the polymer keeping the contrast agent constant changes the precipitate formation significantly. A skilled artisan cannot predict how the change in the amount of the contrast agent in Whalen composition will change the cohesiveness of the precipitate formation. As explained *supra*, it is critical that the composition with higher contrast agent forms a coherent precipitate *in vivo* to minimize fragmentation and possible embolization of unintended vascular sites.

For at least the reasons as stated above, the term "about 40 percent" of Whalen does not anticipate the "greater than 40 to 60 weight percent" of the claimed invention.

In light of the above, withdrawal of this rejection under 35 U.S.C. § 102(e) is respectfully requested.

Claim rejections under 35 U.S.C. §103(a)

Claims 1, 4-8, and 10-16 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Whalen et al. (US 2002/0090339) and Patterson et al. (US 2004/0224864, "Patterson" herein) in view of Evans et al. (US 5,695,480, "Evans" herein).

Applicants traverse the rejection for the following reasons:

Statement of Law

The factual inquiries necessary in an analysis of obviousness by the Office is delineated in MPEP § 2141 as follows:

(A) Determining the scope and contents of the prior art;

(B) Ascertaining the differences between the prior art and the claims in issue;

(C) Resolving the level of ordinary skill in the pertinent art; and

(D) Evaluating evidence of secondary considerations...

MPEP § 2141 further states that:

When applying 35 U.S.C. 103 ...

(A) The claimed invention must be considered as a whole;

(B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and

(D) Reasonable expectation of success is the standard with which obviousness is determined.

The Supreme Court in *KSR International Co.* v. *Teleflex Inc.,* 127 S.Ct. 1727, 1734 (2007), reviewed the analysis for determining if an invention is obvious over the teachings of the prior art and affirmed the factual analysis set forth in *Graham* v. *John Deere Co. of Kansas City,* 383 U.S. 1 (1966). Application of the factual and legal analysis defined by *KSR*, *supra.,* in the context of pharmaceutical inventions was discussed by the Federal Circuit in *Takeda Chem. Indu. Ltd.* v. *Alphapharm Pty. Ltd.,* 83 U.S.P.Q.2d 1169, 1174 (Fed. Cir. 2007), *cert. denied*, 128 S.Ct. 1739 (2008). The Federal Circuit stated that:

> [w]hile the KSR Court rejected a rigid application of the teaching, suggestion, or motivation ('TSM') test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person skilled in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. KSR, 127 S. Ct. at 1731. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis". *Id.* As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry.

Id. Applicants now apply the teachings of the cited art consistent with the applicable standards as set forth by the U.S. Supreme Court, the federal Circuit, and the MPEP and show that Applicants' claimed invention meets the criteria of 35 U.S.C. §103.

1. Scope and content of cited references

The table below illustrates the comparison of the features of the claimed invention with the cited art.

	Biocompatible polymer	**Biocompatible contrast agent**	**Biocompatible solvent**	**Ratio between biocompatible polymer and biocompatible contrast agent**
Claimed invention	2 to 40 weight percent	greater than 40 to 60 weight percent	20 to 58 weight percent (claim 13)	greater than 0.07 or 0.07-0.182
Whalen	2 to 50 weight percent	10 to 40 weight percent	10 to 78 weight percent	No ratio disclosed or explicitly taught
Patterson	1 to 12%	20 to 55%	No specific amount disclosed	No ratio disclosed or explicitly taught
Evans	2.5 to 8 weight percent	10 to 40 weight percent	52 to 87.5 weight percent	No ratio disclosed or explicitly taught

Neither of Whalen, Patterson, or Evans teaches or suggests a ratio of biocompatible polymer to the water-insoluble biocompatible contrast agent to be 0.07 or greater or 0.07-0.182. Additionally, neither of Whalen or Evans teaches or suggests greater than 40 to 60 weight percent of the biocompatible contrast agent.

2. Differences between the claimed invention and cited references

Neither of Whalen, Patterson, or Evans teach or suggest the criticality of the ratio of the polymer and the contrast agent. There is no teaching, suggestion, or motivation in either Whalen, Patterson, or Evans to use a ratio of biocompatible polymer to the water-insoluble biocompatible contrast agent to be 0.07 or greater or 0.07-0.182. Even if the ratios are calculated based on the amount of biocompatible polymer and the contrast agent in each of the cited reference, the compositions taught in Whalen have ratios anywhere from 0.05:1 (20/40) to 5:1 (50/10); the compositions taught in Patterson have ratios anywhere from 0.018:1 (1/55) to 0.6:1 (12/20); and the compositions taught in Evans have ratios anywhere from 0.06 (2.5/40) to 0.8 (8/10). There is no teaching, motivation, or suggestion in either of the cited references to pick a certain ratio of the polymer to the contrast agent, let alone pick and choose a specific number for the ratio as in the claimed invention.

In *Ex Parte Whalen supra.*, the Board ruled that obviousness cannot be proven merely by showing that a known composition could have been modified by routine experimentation or solely on the expectation of success; it must be shown that those of ordinary skill in the art would have had some apparent reason to modify the known composition in a way that would result in the claimed composition. *Id.* at 1084. The Board affirmed the Court ruling in *KSR supra.*, that the obviousness cannot be proven merely by showing that the elements of a claimed device were known in the prior art; it must be shown that those of ordinary skill in the art would have had some "apparent reason to combine the known elements in the fashion claimed." *KSR supra.* at 1741.

Based on the teachings of Whalen, Patterson, or Evans, a skilled artisan would have needed to experiment unduly in picking a specific ratio of the polymer to the contrast agent along with the concentration of the contrast agent to result in a composition with adequate flowability and coherent precipitation *in vivo* without the undesired fragmentation and the shedding of the particles.

The Office makes an erroneous allegation that the amount of contrast agent of greater than 40 to 60 weight percent and the ratio of biocompatible polymer to the contrast agent of 0.07 or greater is a result effective parameter that would be obvious to a person of ordinary skill in the art to routinely optimize. Firstly, the ratio of the polymer to the contrast agent was not recognized in either of the cited references to be a critical parameter. Secondly, it is unpredictable to the skilled artisan if the increase in the amount of contrast agent would result in a cohesive precipitate.

While "the discovery of an optimum value of a variable in a known process is normally obvious," *In re Antonie*, 559 F.2d 618, 620 (CCPA 1977), this is not always the case. One exception to the rule is where the parameter optimized was not recognized in the prior art as one that would affect the results. *Id.*

Here, the Office has not pointed to any teaching in the cited references, or provided any explanation based on scientific reasoning, that would support the conclusion that those skilled in

the art would have considered it obvious to "optimize" the prior art compositions by increasing the amount of contrast agent to be greater than 40- to 60 weight percent and choosing a ratio of 0.07 or greater. On the contrary, a person of ordinary skill in the art will have no reasonable expectation of success in using more than 40% contrast agent and a ratio of greater than 0.07 of polymer to contrast agent since an increase in the concentration of the biocompatible contrast agent can affect any number of variables in the properties of the composition ranging from flowability, coherent precipitation, fragmentation, and visibility. *See* pages 4-5, Example 2, and Figure 1 of the application as filed.

In the absence of any teaching suggestion or motivation in either of the cited references, a skilled artisan would have no reason to choose a ratio of 0.07 or greater or 0.07-0.182 and expect the composition to form a cohesive precipitate.

3. Unexpected results

It was unexpectedly found by the inventors of the instant application that the higher concentration of the water-insoluble, biocompatible contrast agent retains the efficacy of the composition for endovascular surgical procedures by providing adequate flowability through the microcatheter and forming a coherent precipitate *in vivo* without the undesired fragmentation and the shedding of the particles. *See* page 5, paragraph [0021] of the application as filed. As pointed above, it is critical that the composition with higher contrast agent forms a coherent precipitate *in vivo* to minimize fragmentation and possible embolization of unintended vascular sites.

Applicants note that the Declaration by Brian M. Strauss filed February 14, 2008, demonstrates that greater than about 40 to about 60% contrast agent and a ratio of biocompatible polymer to water-insoluble biocompatible contrast agent of greater than 0.055 (greater than 0.07 in instant amended claims) results in a polymer precipitate that is relatively cohesive and provides a high level of visualization during delivery. This is an improved composition over what was known in the art.

Evidence of the cohesiveness of the polymer precipitate formed from embolic compositions of the invention can also be found in the Strauss Declaration. As noted in Example 3 of the instant application, the cohesiveness of the precipitate is measured by determining the amount of particulate shedding. The precipitate is considered cohesive when there are no more than 25 particles per milliliter of test solution measuring greater than or equal to 10 μm or no more than 3 particles per milliliter of test solution measuring greater than or equal to 25 μm. In the Strauss Declaration, samples 1, 2, and 3, with 40.9 % Tantalum and ratio of 0.24 of the polymer to the contrast agent, were shown to be more cohesive that Onyx (20.2 % Tantalum).

For at least the reasons as stated above, this rejection under 35 U.S.C. § 103(a) as being unpatentable over Whalen and Patterson in view of Evans, is in error. Withdrawal of this rejection is respectfully requested.

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

Conclusion

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date June 4, 2009

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